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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/937,296	11/14/2001	Martin Hermann Klemens Brune	2001-1463A	9738

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EXAMINER
STEADMAN, DAVID J

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 05/20/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/937,296	BRUNE ET AL.	
	Examiner	Art Unit	
	David J. Steadman	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 March 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *20,21 and 24-38* is/are pending in the application.

4a) Of the above claim(s) *21,28 and 31-38* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *20,24-27 and 29* is/are rejected.

7)☒ Claim(s) *30* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☒ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Application Status

[1] Claims 20, 21, and 24-38 are pending in the application.

[2] Applicant's amendment to the specification, sequence listing, and claims 20, 21, 30, 31, and 35 in Paper No. 10, filed March 10, 2003, is acknowledged.

[3] Applicant's arguments in Paper No. 10 have been fully considered and are deemed to be persuasive to overcome some of the rejections and/or objections previously applied. Rejections and/or objections not reiterated from previous Office actions are hereby withdrawn.

[4] The text of those sections of Title 35 U.S. Code not included in the instant action can be found in a prior Office action.

Lack of Unity

[5] Applicant traverses the lack of unity (page 5 of Paper No. 10) as set forth in Paper No. 6, which was made final in Paper No. 8. Applicant argues patentability of the claims is irrelevant to restriction. Applicant requests that the examiner point out where it is taught in the MPEP that patentability has relevance to determination of unity of invention. Applicant's argument is not found persuasive. Applicant's attention is directed to MPEP § 1893.03(d) regarding Unity of Invention. MPEP § 1893.03(d) states, "A group of inventions is considered linked to form a single general inventive concept where there is a technical relationship among the inventions that involves at least one common or corresponding special technical feature" and defines "special technical feature" as meaning "those technical features that define the contribution which each claimed invention, considered as a whole, makes over the prior art". Furthermore, according to PCT Rule 13.2, unity of invention exists only when the shared same or corresponding technical feature is a contribution over the prior art. The inventions listed as Groups I-III do not relate to a single general inventive concept because they lack the same or corresponding special technical feature. The technical feature of Group III is a modified NDPK. Based upon applicant's description of the term "extrinsic label" as provided in the specification (see item 11 below for further

information regarding the examiner's interpretation of the term "extrinsic label"), Schneider et al. (*J Biol Chem* 273:11491-11497) teach such a modified NDPK - particularly the NDPK of claim 36, which does not recite the term "extrinsic label". Schneider et al. teaches an NDPK modified to replace phenylalanine with tryptophan at position 64 (page 11492, left column). Schneider et al. teach the fluorescence signal is sensitive to the binding of nucleotide diphosphates (page 11495, left column and Figure 6). Thus, the modified NDPK of Group III, particularly the NDPK of claim 36, is not a contribution over the prior art and thus the inventions of Groups I-III do not have unity of invention.

Applicant argues that Groups I-III as set forth in Paper No. 6 have unity of invention as they all posses the same or corresponding special technical feature, which is the requirement that the NDPK is modified to carry an extrinsic label in both the NDPK's phosphorylated and unphosphorylated forms, which label gives a different detectable signal when the NDPK is phosphorylated from when it is unphosphorylated. Applicant's argument is not found persuasive. It is noted that the modified NDPK of claim 36 is not so limited as does not share this special technical feature. As such, Groups I-III do not share unity of invention for the reasons discussed above.

The requirement is still deemed proper and the examiner reiterates the finality of this requirement.

Claims 21, 28, and 31-38 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a non-elected invention, there being no allowable generic or linking claim.

Specification/Informalities

[6] The objection to the specification for a non-descriptive title is maintained for the reasons of record and the reasons stated below. The objection was fully explained in a previous Office action (see item 2 of Paper No. 8). A new title is required that is clearly indicative of the invention to which the claims are directed. The following title is suggested: "Assay for Nucleoside Diphosphate Using a Modified Nucleoside Diphosphate Kinase Comprising a Fluorescent Label". See MPEP § 606.01 regarding examiner's change in title. Applicant argues (page 5 of Paper No. 10) that amendment to the title has

been deferred in view of the traversal of the restriction requirement. Applicant's argument is not found persuasive. The finality of the requirement has been maintained as Groups I-III do not share unity of invention, and thus, the title of the specification should be amended to reflect the claimed subject matter.

Claim Objections

[7] In view of applicant's failure to respond, the objection to claims 24, 29 and 30 as being dependent upon non-elected claims (see item 3 of Paper No. 8) is maintained.

[8] In view of applicant's failure to respond to the instant objection, the objection to claim 30 (see item 4 of Paper No. 4) is maintained. In the interest of clarity, it is suggested that the term "carrying an IDCC label at position 112" be replaced with, for example, "carrying an IDCC label attached to cysteine at position 112".

Claim Rejections - 35 USC § 112, First Paragraph

[9] The written description rejection of claims 20, 24-27, and 29 under 35 U.S.C. 112, first paragraph, is maintained for the reasons of record and the reasons stated below. The rejection was fully explained in a previous Office action (see item 6 of Paper No. 8). Applicant argues (beginning at the middle of page 5 of Paper No. 10) the rejection does not clearly identify the claim limitation at issue in the rejection. The examiner disagrees with applicant's assertion. It is clear from the rejection as set forth in item 6 of Paper No. 11 that the limitation at issue in regards to the instant written description rejection is the genus of recited modified NDPKs. The rejection states, "[t]he specification teaches the structure of only a single representative species of such modified NDPKs" and "the specification fails to describe any other representative species". Thus, it is clear from the rejection as set forth in item 6 of Paper No. 11 that the limitation at issue is the genus of recited modified NDPKs and the failure of the specification to describe a representative number thereof.

Beginning at the top of page 6 of Paper No. 10 applicant argues the inventors were in possession of the claimed invention at the time the application was filed as the claims and disclosure allegedly teach

that the inventors considered their invention to be applicable to any modified NDPK. Applicant further argues that a single species can be used to support a genus. Applicant cites the following evidence in support of a single species describing an entire genus of modified NDPKs: NDPK enzymes had been cloned from a large number of organisms; an assumption that any NDPK will exhibit a conformational change when phosphorylated; protein chemistry offers numerous methods for detecting conformational changes; extrinsic labels offer more flexible and convenient ways of monitoring conformational changes relative to intrinsic labels, extrinsic labels can be attached to Cys residues, which may require mutagenesis; NDPK sequences are largely conserved and the extrinsic label should be attached in the vicinity of the active site and residues identified in one 3D structure can be mapped to other NDPKs; the necessary mutations should not disrupt enzyme activity; the problems cited by the examiner which might be encountered when mutagenizing a protein are hypothetical and unproven; the inventor's experience with *M. xanthus* NDPK demonstrates that the examiner's problems do not exist in real-world practice; a skilled artisan would have a greater expectation that the invention can be used with NDPKs which do not require mutagenesis; given the inventor's success with IDCC, a skilled artisan would expect other labels to be successful; the examiner has presented no evidence of failure with mutagenesis or other labels and the examiner's theory of failure is disproved by the inventor's success in the most difficult situation; the invention uses a well-characterized enzyme; and the inventor's single species offers guidance for the whole of the recited genus. Applicant's arguments are not found persuasive. It is noted that most of applicant's arguments addressing the written description rejection actually pertain to the scope of enablement rejection under 35 USC 112, first paragraph rejection and not the instant rejection. Applicant's arguments have been addressed to the extent the arguments address the instant rejection. The examiner maintains his position that the single disclosed species fails to describe the entire genus of modified NDPKs. While a single species may fully describe a recited genus, in the instant case it does not. The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical

properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. A representative number of species means that the species that are adequately described are representative of the entire genus. In the instant case, the disclosure of a single species of the recited genus, i.e., *M. xanthus* NDPK with aspartate at position 112 replaced with cysteine carrying an IDCC label, fails to represent the entire genus, particularly in view of the necessity to mutate the *M. xanthus* sequence in order to obtain the recited modified NDPK. Such modifications are highly unpredictable, even within a well-characterized sequence, as a skilled artisan has yet to divine those mutations that may be generated in a given sequence and obtain a desired activity, in this case, maintaining NDPK enzyme activity. As such, one of skill in the art would recognize that the recited genus, having any modification(s) at any position of any NDPK with any amino acid for extrinsic labeling encompasses species that are widely variant in structure. For inventions in an unpredictable art, as is the instant case, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only a single species – more evidence is required to show possession. Given this lack of description of representative species encompassed by the genus of the claim, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention.

[10] The scope of enablement rejection of claims 20, 24-27, and 29 under 35 U.S.C. 112, first paragraph, is maintained for the reasons of record and the reasons stated below. The rejection was fully explained in a previous Office action (see item 7 of Paper No. 8). Applicant reiterates arguments addressing the written description rejection as stated in item 4 above. Applicant's arguments are not found persuasive. Addressing applicant's arguments regarding the scope of enablement rejection, it appears that applicant and the examiner differ as to whether the scope of modified NDPKs and labels used to modify NDPKs is fully enabled by the prior art and the instant specification. The examiner maintains his position that undue experimentation would be required for a skilled artisan to make the entire scope of the claimed invention. While applicant states that their modified and labeled NDPK was

generated "without extensive effort" and that the examiner "has presented no empirical evidence of failure in other enzymes or with modification of other residues or with other labels", it is noted that a skilled artisan would recognize that, particularly in scientific and patent literature, negative empirical evidence of the kind applicant asserts the examiner should present to support his argument, are typically not published and therefore are unavailable. However, to support his position that undue experimentation is required, the examiner has attempted to establish the high degree of unpredictability in performing any modification to an NDPK that results in an NDPK modified to "carry an extrinsic label in both the NDPK's phosphorylated and unphosphorylated forms". As stated during the interview, based on the specification (e.g., see page 4, lines 17-23 of the instant specification), such modifications encompass alterations to the amino acid sequence of NDPK. For example, the specification states that such modifications encompass extrinsic labeling of an NDPK by attachment of IDCC to a cysteine residue (see page 4, lines 23-25 of the instant specification). As stated in a previous Office action, not all NDPKs have a cysteine residue (as evidenced by Izymiya et al. *J Biol Chem* 270:27859-27864) and therefore, a cysteine residue *must* be incorporated to carry IDCC. Applicant has provided guidance for the entire scope of modified NDPKs in the form of a single working example – *M. xanthus* NDPK with aspartate at position 112 replaced with cysteine having an attached IDCC label. Due to the high degree of unpredictability associated with mutating an NDPK amino acid sequence with an expectation of obtaining a protein with the desired activity, in this case maintaining NDPK enzymatic activity, this single working example fails to provide the guidance necessary to enable the entire scope of modified NDPKs. The specification fails to provide guidance regarding the amino acids or regions of all NDPKs that may be modified to carry an extrinsic label without affecting NDPK enzymatic activity. A skilled artisan recognizes that modification to a protein's amino acid sequence can unpredictably alter a protein's characteristics, resulting in a protein with increased activity, decreased activity, loss of activity, or a completely different activity. For example, Witkowski et al. (*Biochemistry* 38:11642-11650) teach that a single amino acid substitution in a beta-ketoacyl synthase completely converted the enzyme to a malonyl decarboxylase (page 11647, Table 1). The specification fails to provide guidance regarding which of the numerous modifications to any NDPK

can be made with an expectation of obtaining the desired activity. Furthermore, while *any* modification to a protein's amino acid sequence carries a degree of unpredictability, a skilled artisan would expect such unpredictability to be higher as NDPK sequences are largely conserved – as acknowledged by applicant (see page 7 of Paper No. 10). Therefore, a skilled artisan would expect that any given NDPK would be highly intolerant of modification due to the conservation of amino acids in NDPKs from a variety of sources. Furthermore, the degree of unpredictability is further compounded by the extrinsic label for detecting dephosphorylation as the choice of extrinsic label is dependent upon the modification to the NDPK. The single working example of a specific label - IDCC - attached to a specific amino acid residue of a specific NDPK - cysteine at position 112 of *M. xanthus* NDPK – fails to provide the necessary guidance for generating a modified NDPK carrying any label. Applicant is invited to provide evidence for predictably modifying any NDPK by any modification to carry any extrinsic label as broadly encompassed by the claims for the examiner's consideration. As such evidence has not been presented in the specification or the prior art and for all the reasons stated in item 7 of Paper No. 8 and the reasons stated above, applicant has not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re* Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re* Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claim Rejections - 35 USC § 103

[11] The rejection of claims 20, 24, 27, and 29 under 35 U.S.C. 103(a) as being unpatentable over Schneider et al. (*J Biol Chem* 273:11491-11497) in view of Deville-Bonne et al. (*Biochemistry* 35:14643-14650) is maintained for the reasons of record and the reasons stated below. The rejection was fully explained in a previous Office action (see item 8 of Paper No. 8). Applicant argues (beginning at page 9 of Paper No. 10) the claims as amended define over the combination of the cited references by

clarification that the label is an extrinsic label. Applicant argues the cited references do not suggest adding an extrinsic label to NDPK to probe its phosphorylation status. Applicant argues that the benefits of using an extrinsic label are not discussed in the cited prior art and assert that the claims are patentably distinct and non-obvious over the cited references. Applicant's arguments are not found persuasive. It is noted that the term "extrinsic label" is not specifically defined in the specification. However, the specification distinguishes an intrinsic label from an extrinsic label by stating, "[r]ather than using properties inherent in the wild-type enzyme, it may be desired to modify the enzyme in some way" (page 4, lines 13-14) and further states, "[o]ne particularly preferred modification is the addition of a fluorescent label" (page 4, line 17). Thus, based on the specification and in accordance with MPEP § 2111, the examiner has interpreted the term "extrinsic label" as being a label, particularly a fluorescent label, added to an enzyme to exploit a property not found within the wild-type enzyme. The combination of references teaches a process of using a *Dictyostelium discoideum* NDPK with a phenylalanine to tryptophan mutation at position 64 for monitoring the fluorescence of the dephosphorylation of the phosphorylated intermediate due to the addition of ADP. The replacement of phenylalanine with tryptophan at position 64 of *D. discoideum* NDPK would incorporate a fluorescent label into *D. discoideum* NDPK to exploit fluorescence of tryptophan 64 - a property that is not found in the wild-type enzyme as wild-type *D. discoideum* NDPK exhibits fluorescence due only to tryptophan at position 137. Therefore, claims 20, 24, 27, and 29, drawn to a process for detecting nucleoside diphosphates as described above would have been obvious to one of ordinary skill in the art for all the reasons as set forth in item 8 of Paper No. 8 and the reasons stated above.

Conclusion

[12] Claims 20, 21, and 24-38 are pending.

[13] Claims 21, 28, and 31-38 are withdrawn from consideration.

[14] Claims 20, 24-27, and 29 are rejected.

[15] Claim 30 is objected to for the reasons set forth in items 7 and 8 above.

[16] No claim is in condition for allowance.

Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Steadman, whose telephone number is (703) 308-3934. The Examiner can normally be reached Monday-Thursday from 6:30 am to 5:00 pm. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Ponnathapura Achutamurthy, can be reached at (703) 308-3804. The FAX number for this Group is (703) 308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Art Unit receptionist whose telephone number is (703) 308-0196.

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Patent Examiner
Art Unit 1652

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